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Original Research

The distinctive role of systemic immune-inflammatory parameters in gestational trophoblastic diseases

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Abstract

Aim: In this study, we aimed to distinguish molar pregnancies from healthy pregnancies with the parameters that make up simple hematological tests that can be easily applied in the routine and to increase diagnostic sensitivity.

Material and Methods: This retrospective cohort study was conducted between January 2018 and September 2022 at the University Hospital Gynecology Clinic. The study included 80 partial hydatidiform moles (PMH), 45 complete hydatidiform moles (CMH) and 50 healthy pregnant women. Before surgical curettage in molar pregnants and in routine antenatal examinations in healthy pregnant women, white blood cell (WBC) counts, neutrophil (NC) counts, lymphocyte (LC) and platelet counts (PLT), red cell distribution width (RDW), mean platelet volume (MPV), platelet distribution width (PDW), hemoglobin (Hb) and fibrinogen results were recorded. The Neutrophil-lymphocyte ratio (NLR), Platelet-lymphocyte ratio (PLR) and systemic immune-inflammatory index (SII) were calculated based on the results of complete blood count.

Results: WBC [8.5±2.30] vs [10.2±5.6]103/mm3, NC [6.05±5.56] vs [7.5±6.05]103/mm3, PDW [16.59±0.9] vs [16.87±0.75]% in PMH and CMH groups, respectively and NLR [3.23±2.4] vs [3.61±3.1], Fibrinogen [354±79]vs[347±82] mg/dl and SII [689.2±76.1] vs [701.16±52] were measured. These parameters were found significantly higher in molar pregnancy group then the controls. However, MPV [10.4 ± 0.1]fL and RDW [14.5 ±1.21] % values were significantly higher in healthy pregnancies than in molar pregnancies ($p<0.05$ for two parameters).

Discussion: A higher inflammatory response is observed in molar pregnancies than in healthy pregnancies due to uncontrolled trophoblastic growth. Accelerating the diagnosis of GTD allows for early treatment with simple prognostic variables available from the measurement of peripheral blood cells.

Keywords

Blood Cells, Mole Hydatiform, Trophoblastic Disease

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Introduction

Gestational trophoblastic diseases (GTD) are a group of diseases that develop as a result of abnormal fertilization and are characterized by abnormal, excessive proliferation of trophoblasts. It has a wide range from a hydatidiform mole that originates from the placenta and may result in spontaneous resolution to life-threatening choriocarcinoma [1-3]. Hydatidiform mole (HM) is the most common form of GTD. It consists of two clinical forms that differ from each other in different cytogenetic, histological, clinical and prognostic features: PHM with 1-4% less invasion and malignant potential, and CMH with 15-20% higher risk of invasion and malignancy [4].

Progress in ultrasonographic imaging (USI) and easier and more sensitive measurement of beta human chorionic gonadotropin (β-hCG) levels have facilitated the diagnosis of molar pregnancy. The characteristic USI for CMH is in the first trimester; It is a "snowstorm"-looking placenta formed by vesicles formed as a result of hydropic swelling of the chorionic villi in the absence of fetal tissue and amniotic sac. The characteristic USI for PMH is a large placenta with a "Swiss cheese" appearance, with focal cystic spaces in the placental tissues. Despite all these findings, it is difficult to diagnose with only USI and β-hCG in early pregnancy [5,6]. GTD includes trophoblastic diseases with varying degrees of malignant potential. GTN can occur after molar or non-molar pregnancies. Today, it is the most cured gynecological malignancy, and programmed follow-up is critical in the management of the disease [4].

New parameters such as NLR, PLR, which are formed by formulating simple blood count parameters (CBC), which are various non-invasive markers, have started to be used as systemic immune response markers (SIR) in most pathological inflammations and malignancies [7,8]. In various studies, it has been shown that decidual trophoblastic cells behave like cancer cells due to their proliferative, migratory and invasive properties and share the same common molecular features. Inflammation brought about by angiogenesis, invasion, and metastasis leads to lymphocytosis, neutrophilia, thrombocytosis, and lymphocytopenia [9,10].

The aim of the study to explain the pathophysiological mechanisms of molar pregnancy with parameters that can be easily applied in routine and simple hematological tests and to increase its diagnostic sensitivity in distinguishing it from healthy pregnancies.

Material and Methods

The study was carried out at the University Hospital Gynecology Clinic between January 2018 and September 2022. A total of 125 patients aged between 18-45 years, who were followed up and treated for the diagnosis of mole hydatidiform (PMH: n=80; CMH: n=45) and 50 healthy first trimester pregnant women were included in the study. Study inclusion criteria were defined as positive pregnancy test, gestational age of<12 weeks, healthy singleton pregnancy, final pathology result, CMH and/or PMH, respectively. Pregnant women with an ectopic pregnancy, a history of chronic systemic disease, disorders in bleeding parameters, using anti-inflammatory drugs, and those with a positive result for malignancy were excluded from the study. Mole hydatidiform pregnancy was diagnosed by pathological examination of curettage material. Demographic characteristics and CBC parameters of the patients were recorded at their first hospitalization before vacuum curettage. NLR, PLR and SII were calculated according to laboratory results (NLR = neutrophil count/lymphocyte count ratio; PLO =platelet count / lymphocyte count ratio; SII = platelet count x neutrophil count / lymphocyte count). This study was approved by the institutional review board (2011-KAEK-25 2022/09-14).Written informed consent was obtained from all participants.

Statistical Analysis

SPSS (ver.23) program was used for statistical calculations. Statistical comparisons between groups were performed using the Student's t-test and the Mann-Whitney U test. Descriptive data were expressed as mean values and standard deviation. The statistical significance level was accepted as 0.05.

Ethical Approval

Ethics Committee approval for the study was obtained.

Results

In the group of 125 molar pregnancies included in the study, 80 patients had PMH (66.6%) and 45 patients (33.4%) had CMH final pathology results. Arh (+) was the most common blood group in 32.4% of the patients, and ARh (-) was the least common blood group in 1.5% of the patients. Only in CMH patients, the pre-curettage β-hCG level was statistically significantly higher (p=0.087). There was no statistically significant difference between molar pregnancy groups in terms of demographic characteristics (p<0.05) (Table 1).

WBC [8.5 ± 2.30] vs [10.2±5.6]103/mm3, NC [6.05±5.56] vs [7.5±6.05] 103/mm3, PDW [16.59±0.9] vs [16.87±0.75] % in PMH and CMH groups, respectively and NLR [3.23±2.4] vs [3.61±3.1], Fibrinogen [354 ±79]vs [347±82] mg/dl and SII [689.2±76.1] vs [701.16±52] were measured. These parameters were found significantly higher in molar pregnancy group then the controls. However, MPV[10.4±0.1] fL and RDW[14.5±1.21]% values were significantly higher in healthy pregnancies than in molar pregnancies (p<0.05 for two parameters). There was no statistical difference between the 3 groups in terms of Hb,PLT, LC and PLR (p>0.05 for all parameters (Table 2).

Discussion

Table 1. Demographic characteristics of molar pregnancy groups

Variables	Partial Mole Hydatidiform (n=80) (X ± SD)	Complete Mole Hydatidiform (n=45) (X ± SD)	p
Age (year)	28.47±7.5	31.19±9.55	0.352
Gravidity (n)	2 .67±1.45	3.62±1.60	0.451
Parity (n)	1.41±1.24	1.55±1.25	0.562
Abortus (n)	0.4±0.49	0.4±0.50	0.433
Gestational Week	8.15±2.21	8.41±2.7	0.57
Preop.hcg (IU/ml)	46010 ±59100	76290±93080	0.087

SD: standard deviation. Descriptive analyzes are presented using (X ± SD), *p<0.05 was considered significant

Table 2. Statistical analysis of subgroups of the study population

Variables	Partial Mole Hydatidiform (n=80) (X ± SD)	Complete Mole Hydatidiform (n=45)(X ± SD)	Non-Molar Pregnancy (n=50)(X ± SD)	p
Hemoglobin (gr/dl) #	11.9±1.36	11.26±1.75	11.8±1.8	0.11
White blood cell# count (×10³/mm³)	8.5 ±2.30	10.2±5.6	8.4±3.1	<0.004
Neutrophil# count (×10³/mm³)	6.05±5.56	7.5±6.05	5.9±2.25	<0.001
Lymphocyte# count (×10³/mm³)	2.01±0.85	2.15±1.85	2.10±1.96	0.074
Mean platelet volume* (femtoliter)	9.43±1.18	9.45±1.46	10.4±0.1	<0.001
Platelet distribution width# (%)	16.59±0.9	16.87±0.75	16.26±1.47	<0.013
Red cell distribution width# (%)	13.81±1.6	13,68±1,08	14.5 ±1.21	0.029
Platelet count (×10³/mm³) *	229.1±64.8	201.2±59.2	220±59	<0.327
Neutrophil/Lymphocyte ratio#	3.23±2.4	3.61±3.1	2.66±1.26	<0.001
Platelet/Lymphocyte ratio#	136±54	142±87	117±59	0.45
Fibrinogen#(mg/dL)	354 ±79	347±82	307±51	<0.021
SII	689.2±76	701.1±52	618.1±64	<0.042

SD: standard deviation. Descriptive analyzes are presented using (X ± SD), Student's t-test *p<0.05 and Mann-Whitney U test #p<0.05 was considered significant.

Molar pregnancies and gestational trophoblastic neoplasia (GTN) originate from placental trophoblasts. After excessive abnormal uncontrolled proliferation and invasion of these trophoblasts, GTN occurs [1,2,10]. Decidual implantation, myometrial invasion and abnormalities in immunological tolerance are also blamed in the etiology of GTN. The pathophysiological mechanism underlying molar pregnancies is still unclear. In CMH, lack of villous trophoblast development and defective placentation due to endovascular trophoblastic invasion may lead to inadequate development of the placental decidual interface. However, the presence of maternal genome in PMH may be a reason for adequate interaction between trophoblasts and the decidual layer, according to CMH. This may be due to an inadequate inflammatory response to enhanced trophoblastic invasion in GTD [11,12].

MPV and PDW, indicative of early platelet activation, and platecrit have been associated with conditions with thrombosis and inflammation. The increase in these values is associated with ongoing inflammation. Interpretation of MPV and PDW together is much more effective in the evaluation of platelet activation. Increased platelet count and aggregation allow the tumor to escape from the immune response [13]. With increased inflammatory response and abnormal syncytiotrophoblast activation, dilutional thrombocytopenia due to increased intravascular volume and increased MPV and PDV values are seen in preeclampsia, hyperemesis gravidarum and GTD, which are placental invasion anomalies compared to healthy pregnancies [14]. While leukocytosis develops as a result of the ongoing inflammatory process, adhesion molecules are released into the circulation as a result of this activation and various immune mediators become evident during pregnancy from implantation. Eskicioglu et al. in their study between women with molar pregnancies and women with healthy pregnancies, found decreased PDW levels and WBC values, and found no difference in platelet and MPV values. These results has been atributed due to the loss of cytotrophoblast invasion in complete molar pregnancies [15]. Unlike this study, Aiob et al. in their study comparing molar pregnancy and missed abortion, observed a higher neutrophil level in molar pregnancies [16]. We also found a statistically significant increase in WBC and NC in the molar pregnancy group in this study. This increase was not significant between partial and complete molar pregnancy subgroups. This result suggests that molar pregnancies may cause a higher inflammatory response due to continued trophoblastic growth. In the study by Yayla et al. in which they compared molar pregnancies and healthy pregnancies, they found low MPV, PDW, WBC and an increase in NC, similar to our study [17].

Another marker used in the clinic RDW is a parameter that shows the distribution of erythrocyte volume; it has been shown to increase as a result of defective erythropoiesis, increased inflammation, or hemolysis. Zhang et al. stated an increase in RDW and platelets in invasive moles and attributed the increase in these parameters, which increased in the inflammatory circulation, to the primary immune response secondary to changes in the hemopoietic activity in the bone marrow [18]. In this study, however, there was no significant difference in platelet count between molar pregnancy and healthy pregnancy, while RDW value was found to be low in molar pregnancies, unlike this study.

The neutrophil- to- lymphocyte ratio is a quick and simple test to reach the result, which is accepted as a marker of the body's immune response to foreign agents. Various studies have reported increased NLR as a predictor of outcomes in trophoblastic endometrial precancerous and cancerous lesions with abnormal uterine bleeding [19]. Guzel et al. suggested that NLR was higher in women who developed invasive moles than in women who did not, and could be used as a biomarker of invasion in GTD [20]. Genc et al. also found NLR to be statistically significantly higher in the molar pregnancy group in their study on hydatidiform mole, healthy pregnancy and non-pregnant gynecology groups [21]. In the current study, we found that the NLR value was higher in the molar pregnancy group compared to the healthy pregnancies, but we did not find a statistically significant difference between the groups in another marker, PLR.

SII, which is another recent new inflammatory index, calculated from platelet, neutrophil and lymphocyte counts, is a much more important marker in demonstrating inflammation and immune response compared to PLR and NLR. Studies have shown that high SII values are associated with disease severity and poor prognosis in many diseases and malignancies [22].

In this study, we found that the SII value is significantly higher in molar pregnancies than in healthy pregnancies, especially in complete moles. The increase in this parameter is the immune response of blood cells to physical stress in molar pregnancies; oxidative stress and inflammation can cause such systemic consequences.

Conclusion

There are few studies that have examined inflammatory markers that make up the parameters of the CBC with a sufficiently large number of cases of GTD. The significant differences in PDW and MPV, which are indicators of platelet activation in the current study, suggest that molar pregnancies require less PLT activation compared to intrauterine pregnancy requiring adequate and healthy endometrial invasion. At the same time, high leukocyte counts, NLR and SII values we detected in molar pregnancies indicate an increased inflammatory response in the etiopathogenesis of GTD. With simple prognostic variables available from CBC counts widely available in clinical practice, even in countries with limited health resources around the world, accelerating the diagnosis of GTD could enable early diagnosis and treatment, while at the same time preventing female deaths and adverse outcomes.

The main limitations of this study are its single-center, retrospective design and relatively small sample size.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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